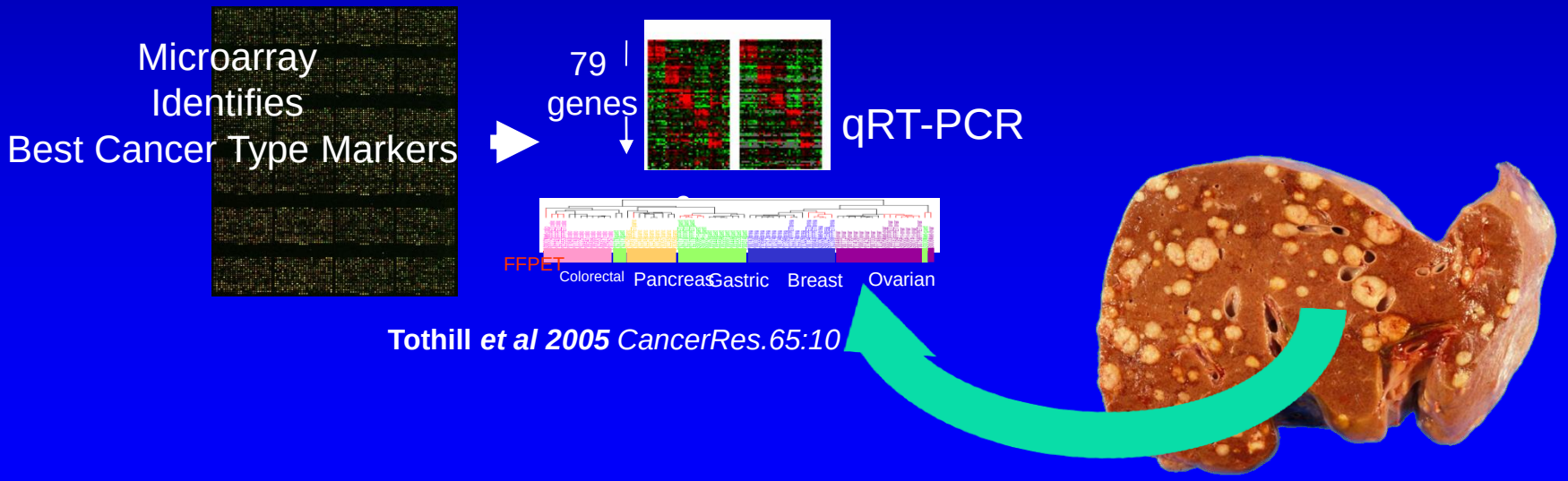
Latest research / Update : UK CUP-ONE

Harpreet S. Wasan
Consultant / Reader in Medical oncology
Department of Cancer Medicine
Hammersmith Hospital, Imperial College London
h.wasan@imperial.ac.uk



CUP 2015: Improving Patient Management & Outcomes
Royal Royal College of Physicians, London Sept 2015

My Disclosures in respect of this talk (CUP)

bioTheranostics, (BioMerieux / Pasteur Foundation) :
- Advisory Board (uncompensated)
- Research funding within CUP-ONE Trial

Topotargets A.S : - Advisory Board (uncompensated)

Astra Zeneca : - Advisory Board (uncompensated)

Jo's Foundation (CUP charitable trust):
- Medical Advisor (uncompensated)
- Research funding

NICE CUP Guidelines CG104
: - Medical input to advisors (uncompensated)

CRUK : Research funding

Merck KGA : Research funding (COIN-B), biomarker development and advisory boards

UK UPDATE CUP RESEARCH

- **UK CRUK NCRI CUP-ONE Trial**
  - 'Best' Tissue based test for site-of-origin
  - Patient Outcomes (OS, predictive Biomarkers)
    - Untreated
    - Treated as site- specific
    - Treated as CUP

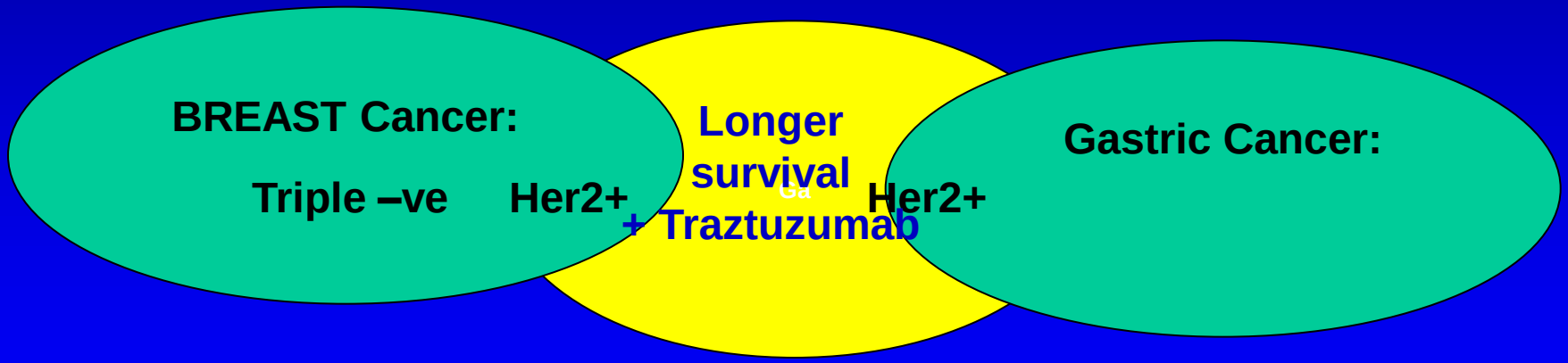
- **Other Research & Trials (proposed)**
  - Audits from CUP/MUO MDT's
  - NHSE GECIP 100K Genome

- **Dynamic cancer models :**
  - Lessons from treating solid cancers

Cancer of Unknown Primary: Paradigm for future as model for treatment direction of *all* metastatic disease?

- Molecular Heterogeneity has major clinical implications for ***treatment***

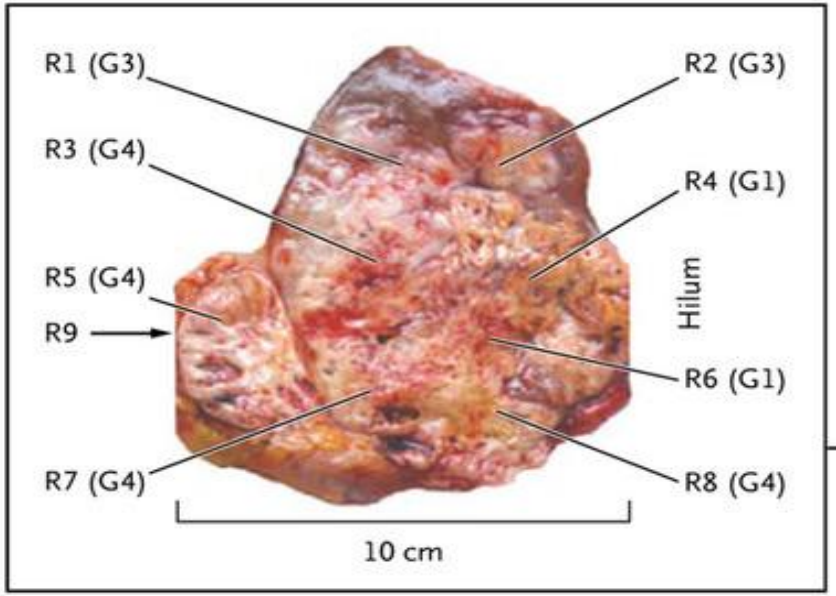
  (*more* than site of origin)

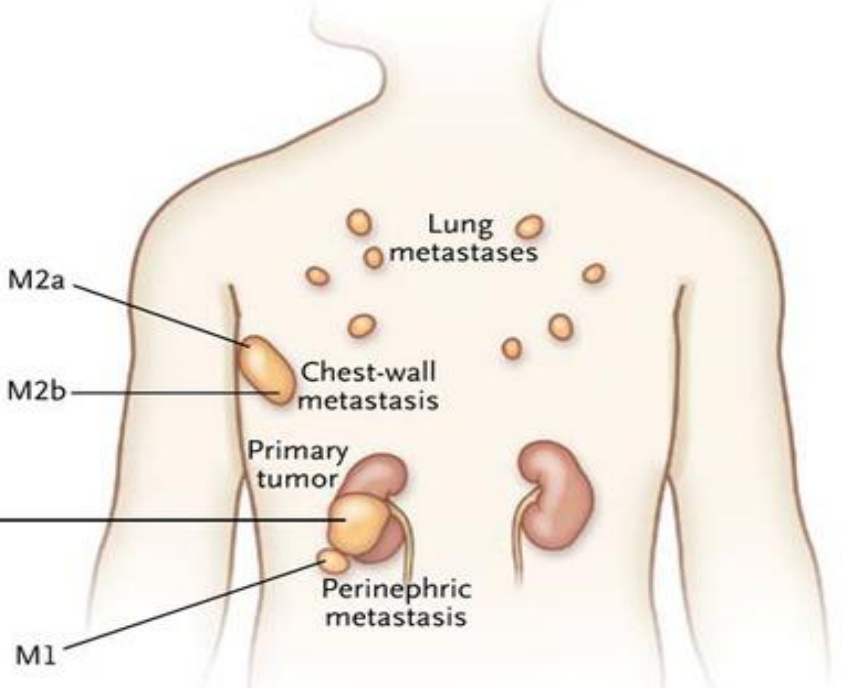


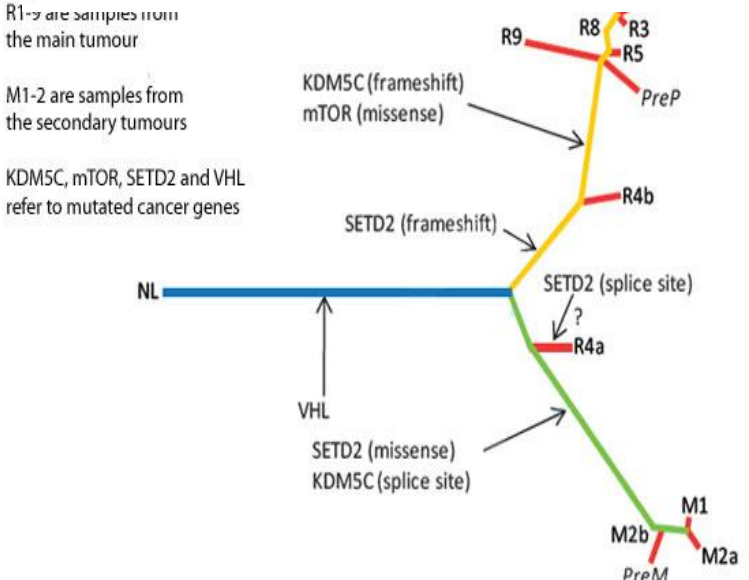
- Phase II study promise ….

  …Phase III failure phenomenon

are multiple biopsies important? : Tumours are heterogeneous







101 nonsynonymous point mutations and 32 indels

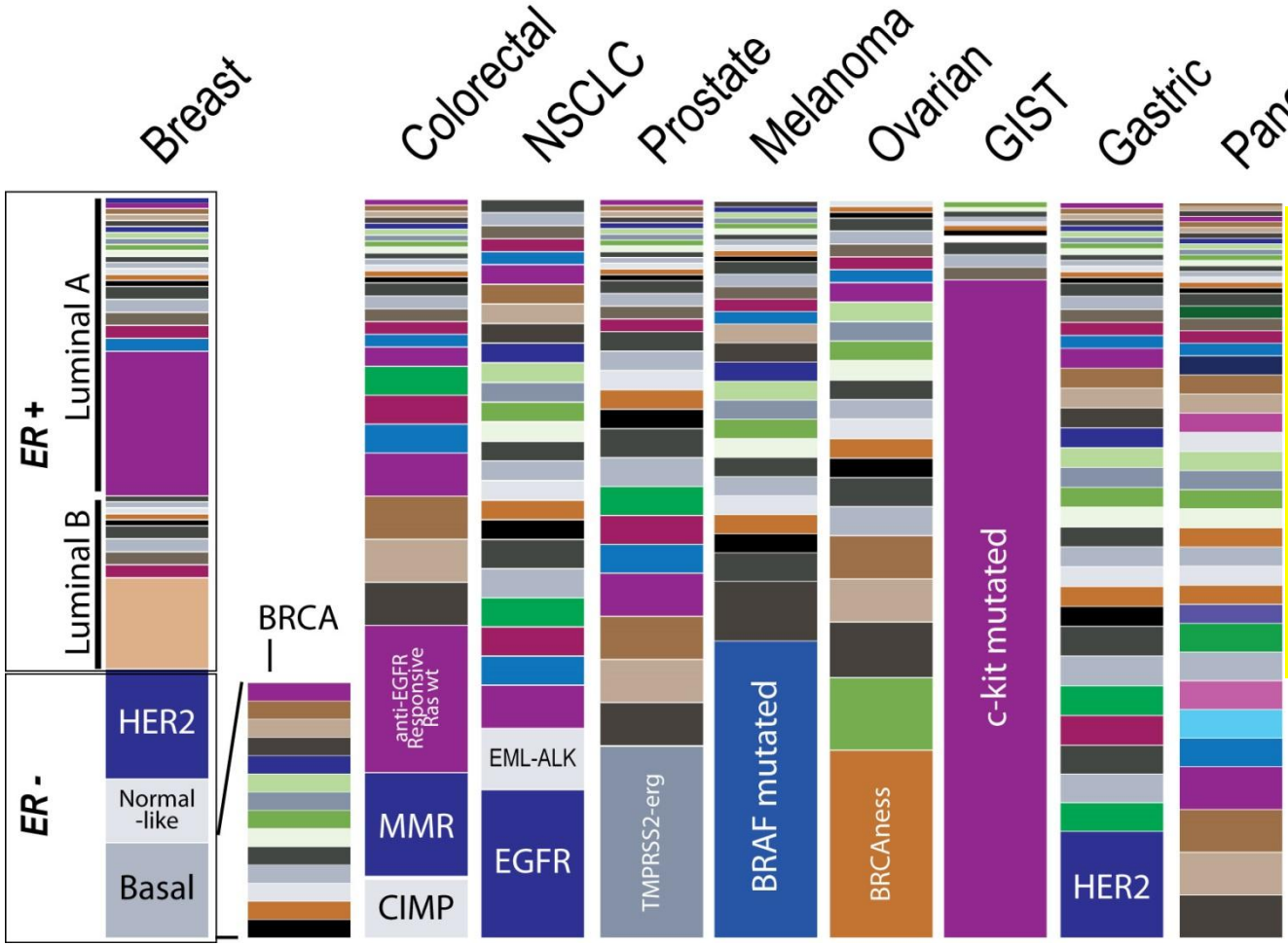
133 significant (?) changes in 10 biopsies

"Intratumor heterogeneity can lead to underestimation of the tumor genomics landscape portrayed from single tumor-biopsy samples and may present major challenges to personalized-medicine and biomarker development"

Intratumor Heterogeneity and Branched Evolution Revealed by Multiregion Sequencing. Gerlinger et al. NEJM 2012

Emerging Molecular Taxonomy by "Site of Origin " - Traditional

Potentially many low prevalence phenotypes



RESPONSE prediction to Biomarker

? uncommon

Challenges

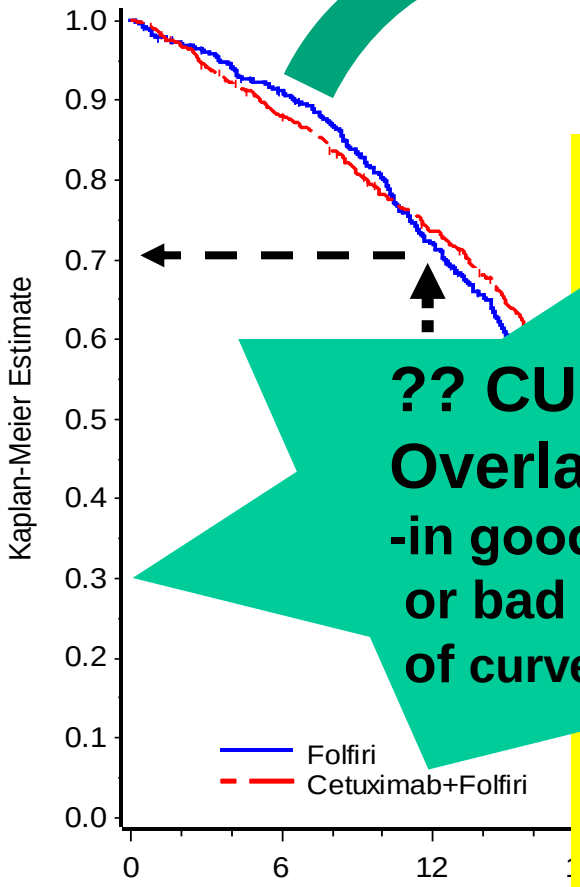
CUP Patient 45y male PS-2 :

- liver + peritoneal + bone metastases
- Liver Bx G3 adenocarcinoma, sCEA-120, Anemia,
  CT mass ?? in ascending colon:
  Colonoscopy (adequate X2) negative …
  MDT – Path consistent with lower GI origin
  Bio-T SOO Expression Profile – prob CRC

No response to first line
FOLFOX-Bevacizumab (RAS-mut)

Where is this patient on the curve ?

CRYSTAL Trial metastatic CRC : OS in ITT Population :
where would a MUO ~ CRC fit?



?? CUP-"CRC" Overlap
-in good ('wished') or bad part (++) of curve (or both)

30% of the population are not surviving beyond a year!

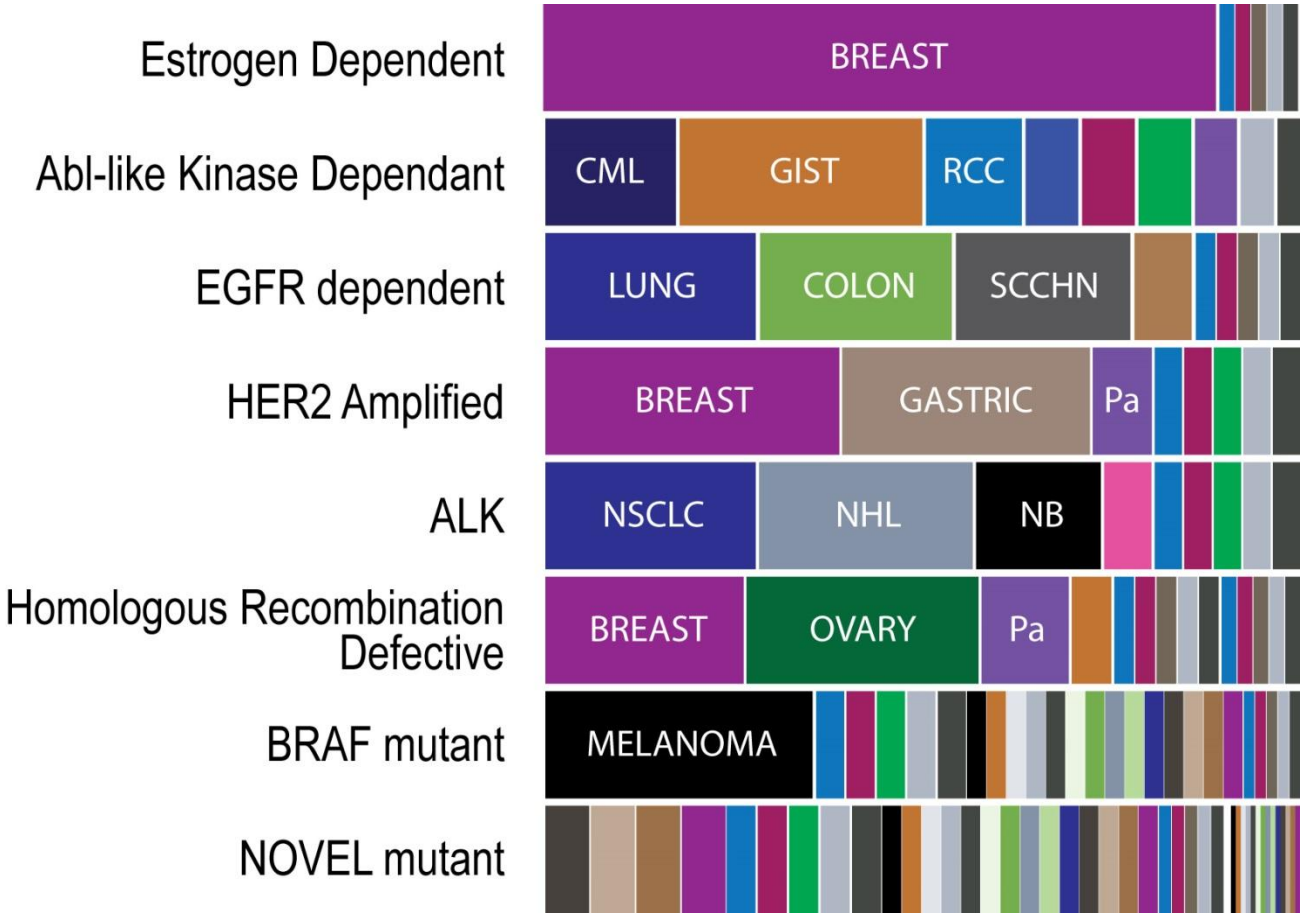
cancer this represents a t population burden

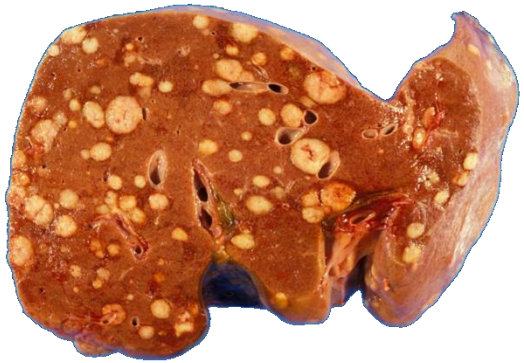
bsets not really ional Response colorectal cancer" ??

At Risk											Overall Survival Time (months)
Folfiri	599	534	414	283	197	138	97	67	20	3	0
Cet+FIRI	599	520	427	319	220	160	125	97	33	6	0

Molecular Taxonomy – Cancer "Biotypes"

independent of "Site of Origin " - Future





CUP ONE TRIAL :

A multi-centre phase II trial to assess

- the efficacy of epirubicin, cisplatin and capecitabine in carcinomas of unknown primary (CUP):

- incorporating the prospective validation of molecular classifiers in diagnosis and classification and exploratory metabonomics

UK CUP-ONE:
evolution of Clinical & research Framework

- NCRN Upper GI /HPB group 2004 +
- CTAAC full application / Glasgow CTU
  - Randomised clinical study *not* supported due to accrual concerns
  - TRICC application: Awarded Jan 2007
- **Planned start was Nov'09 - actual Feb 2010**
  - 16+ Centres with expression of interest
  - Drug Funding – AZ collaboration ?Vandetanib
- NICE UK CUP Clinical Guidance 2010
  - Acute Oncology service review
- **Trial accrued Target 400 2014**

CUP ONE Trial evolution…..

……. Japan Vs South Africa !

UK CUP-ONE:
evolution of Clinical & research Framework

- **Trial accrual Target 400 2014**

- **Trial accrual Target increased 2014**
  - **Part 1 ECX clinical Phase II completed 2013**
  - **Tissue QA guidance : IDMC 2014**
    - **Extend Recruitment-**
    - **624 final recuitment – Closed Dec 2014**
      - some larger centres e.g. Manchester not open until 2014

CUP-ONE Trial has two parts: clinical and translational

- Translational part of trial
  - Uncertainty (at *any*-time of patient Pathway)
  - Bx available- 'split into 3'
  - compares (double-blinded) –
    - best currently available IHC tools at the highest standard

    Vs
    - Modern molecular diagnostics
      - Biotheranostics CancerTypeID
        - V Healthscope CUPGuide Peter MacCallum Cancer Center
  - up to 400 patients assessable

- Erlander, M.G., et al., *Molecular classification of carcinoma of unknown primary by gene expression profiling from formalin-fixed paraffin-embedded tissues.* J Clin Oncol, 2004. **22**(14S): p. 9545.
- Tothill, R.W., et al., *An expression-based site of origin diagnostic method designed for clinical application to cancer of unknown origin.* Cancer Res, 2005. **65**(10): p. 4031-40
- Dennis, J.L., et al., *Markers of adenocarcinoma characteristic of the site of origin: development of a diagnostic algorithm.* Clin Cancer Res, 2005. **11**(10): p. 3766-72.

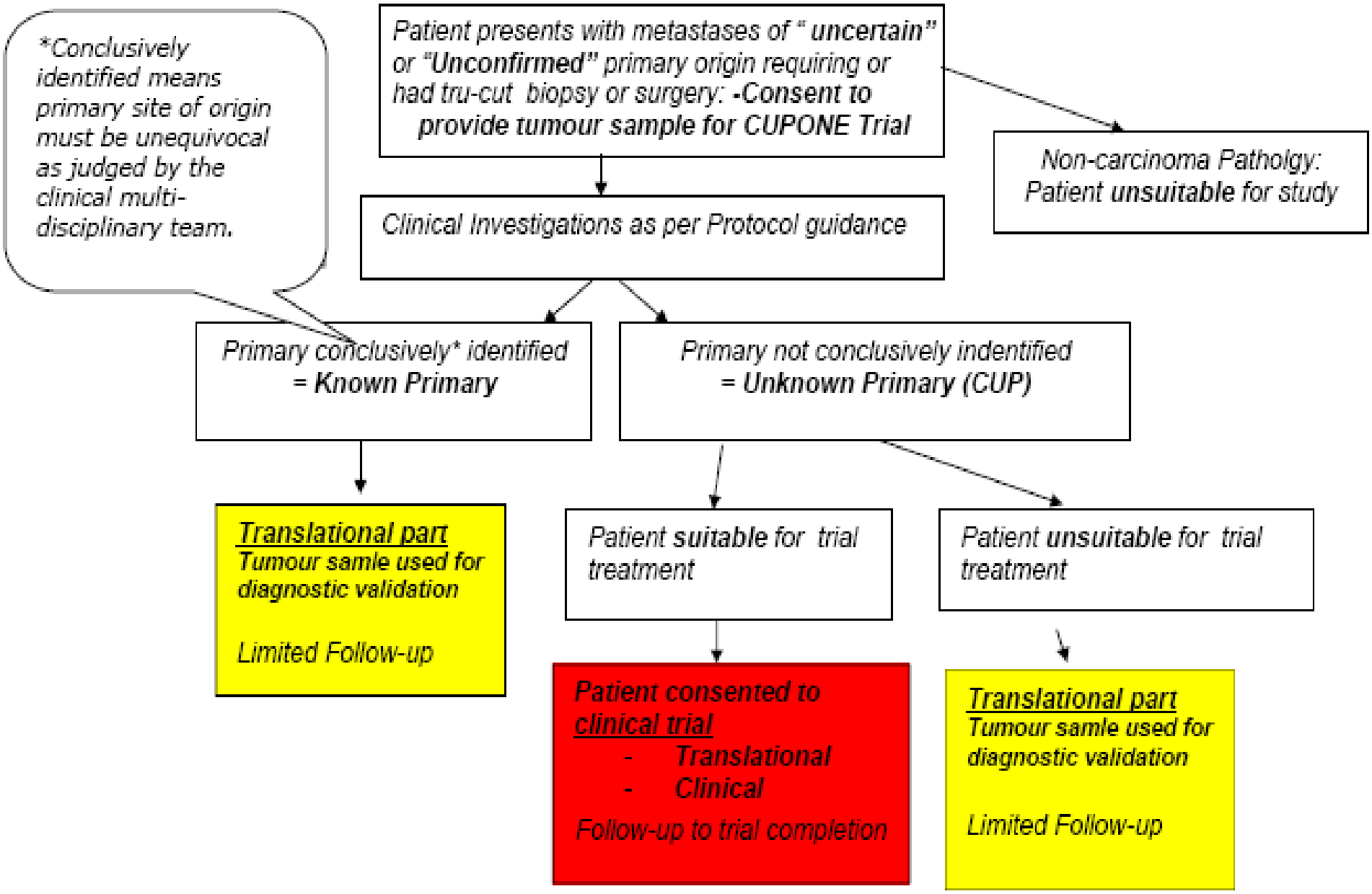
CUP-ONE Trial has two parts: clinical and translational

- Clinical part of trial
  - CUP by exclusion of known primary
  - Phase II epirubicin, cisplatin, capecitabine
    - 20 patients : Futility / safety analysis
    - 56 patients : efficacy analysis
    - off-trial Chemotherapy regimens & survival data

      - up to 400 patients assesable

      - Clinical – molecular predictive & prognostic correlates
    - ? randomised Phase II –
      - Vandetanib maintenance (AZ-NCRN) never happened

CUP ONE: Study Schema



CUP-ONE Study Objectives

- **Primary objective:**

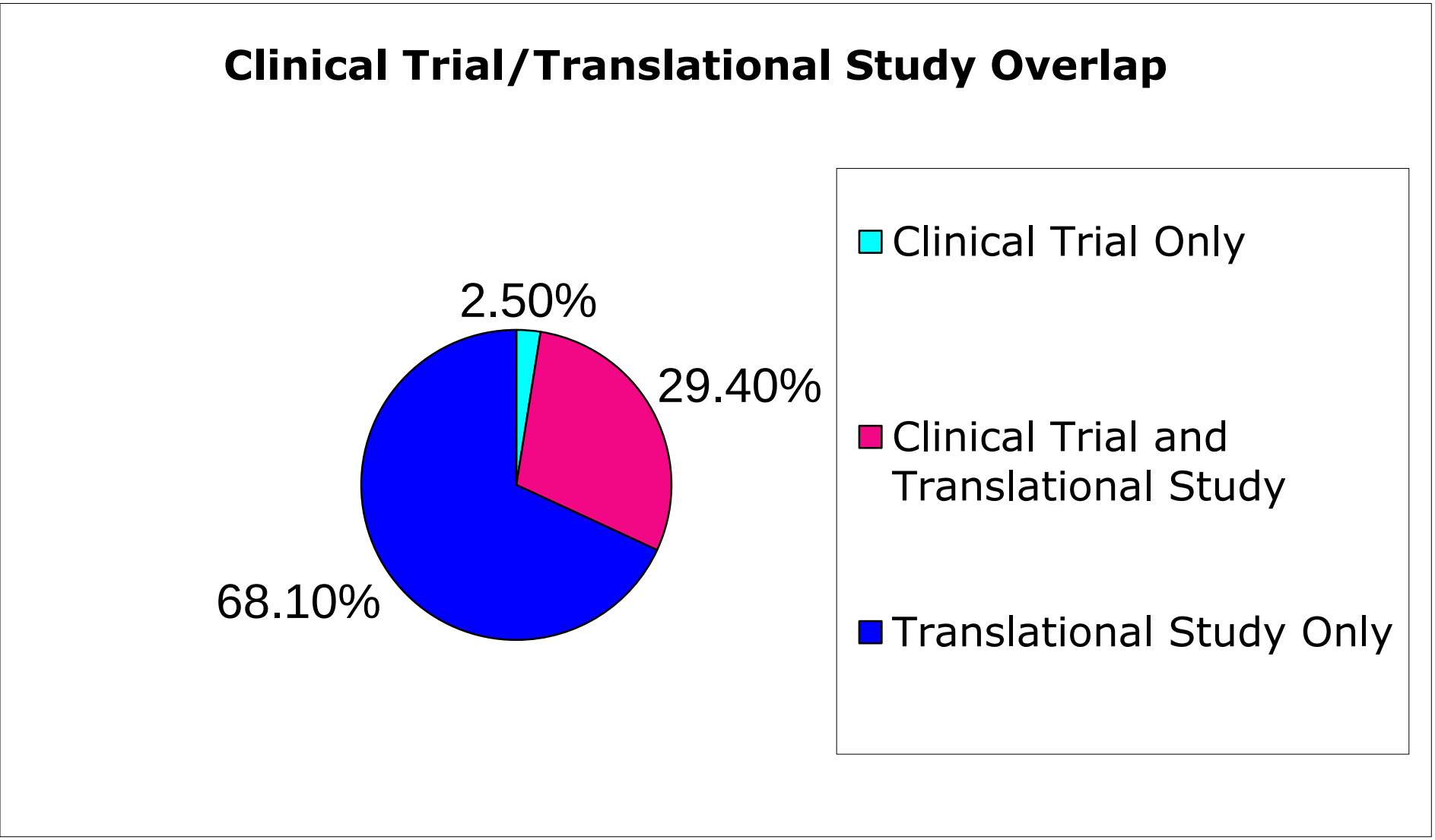
  - For **translational** part primary objective is to select the molecular classifier with the highest diagnostic accuracy
    (expecting at least 50%% knowns)

  - For the **clinical** trial the primary objective is to estimate the response rate with ECX (+/- biological)

- **Secondary objective: Both parts of Trial**

  - Progression-free survival (clinical)
  - Overall survival
  - Quality of life
  - Cost utility comparison of diagnostic molecular classifiers with average clinical diagnostic work-up
  - Correlation of molecular profiles with patient outcome
  - To assess utility, relevance and necessity of clinical investigations in CUP, in comparison to molecular classifiers

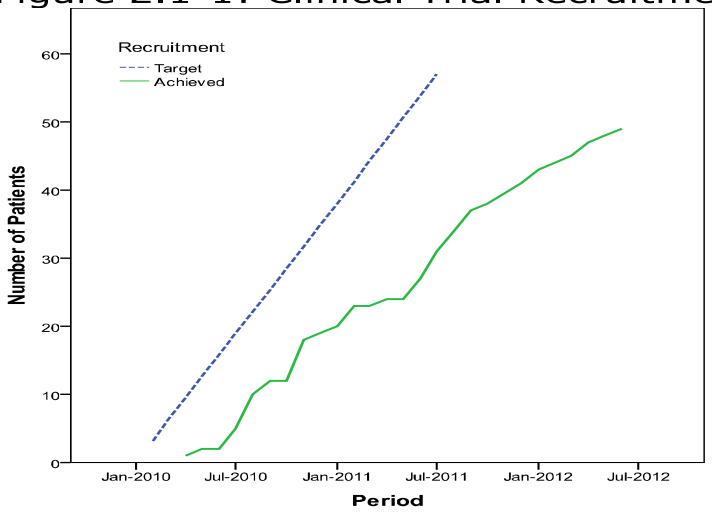
CUP ONE: Clinical Trial Recruitment



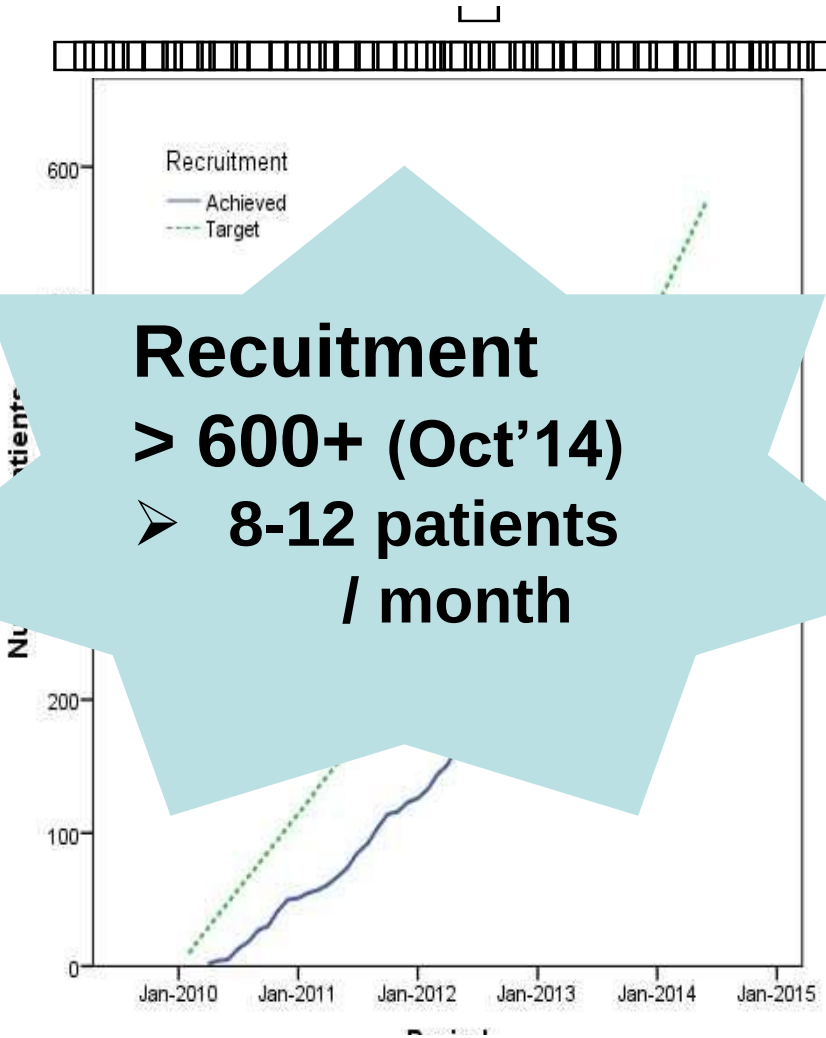
CUP ONE: Trial Recruitment Q4 2014

Temp stopped futility analysis

Figure 2.1-1: Clinical Trial Recruitment



Recuitment
> 600+ (Oct'14)
- **8-12 patients / month**



Clinical

Translational

Clinical outcomes from the UK CUP-ONE Study: A multi-centre trial to assess the efficacy of Epirubicin, Cisplatin and Capecitabine (ECX) in carcinomas of unknown primary (CUP) with prospective validation of molecular classifiers

CUP-ONE combines a multicentre phase II trial of an ongoing translational study [Part 1] incorporating blinded prospective validation of 3 diagnostic molecular classifiers, and treatment with epirubicin, cisplatin and capecitabine (ECX) [Part 2].

Recruitment: Since February 2010, CUP-ONE has recruited 592 patients to the Part 1 translational study (ongoing) and 59 to the clinical trial Part 2 (54 assessable in both parts). Part 2 closed to recruitment in February 2013. Results are presented for 58 eligible patients.

Study population:

Male 47%, female 53%

ECOG PS 0: 38%, 1: 62%

Median age: 63 (range 29-78)

93% Stage IV, 5% Stage III

81% adenocarcinoma, 5% squamous carcinoma, 50% poorly/undifferentiated pathology

Treatment response (RECIST 1.1):

•The best overall response rate was 35% (90% confidence interval 26%-46%), which rejects the null hypothesis of 20% (p=0.006).

•The second evaluation demonstrates that additional continued responses are seen beyond 12 weeks in up to a quarter of patients.

Progression-free survival and overall survival

•Median PFS is 30 weeks, 80% CI: (25 and 33 weeks)

•Median OS is 44 weeks, 80 % CI: (30 and 48 weeks)

CUP ONE TRANSLATIONAL STUDY

The CUP-ONE trial and translational study - 592 patients in total and 59 Part 2 (clinical) patients.

The following data about site of CUP biopsy are from 24 of the 59 tissue samples so far sectioned and despatched to investigators for molecular analyses.

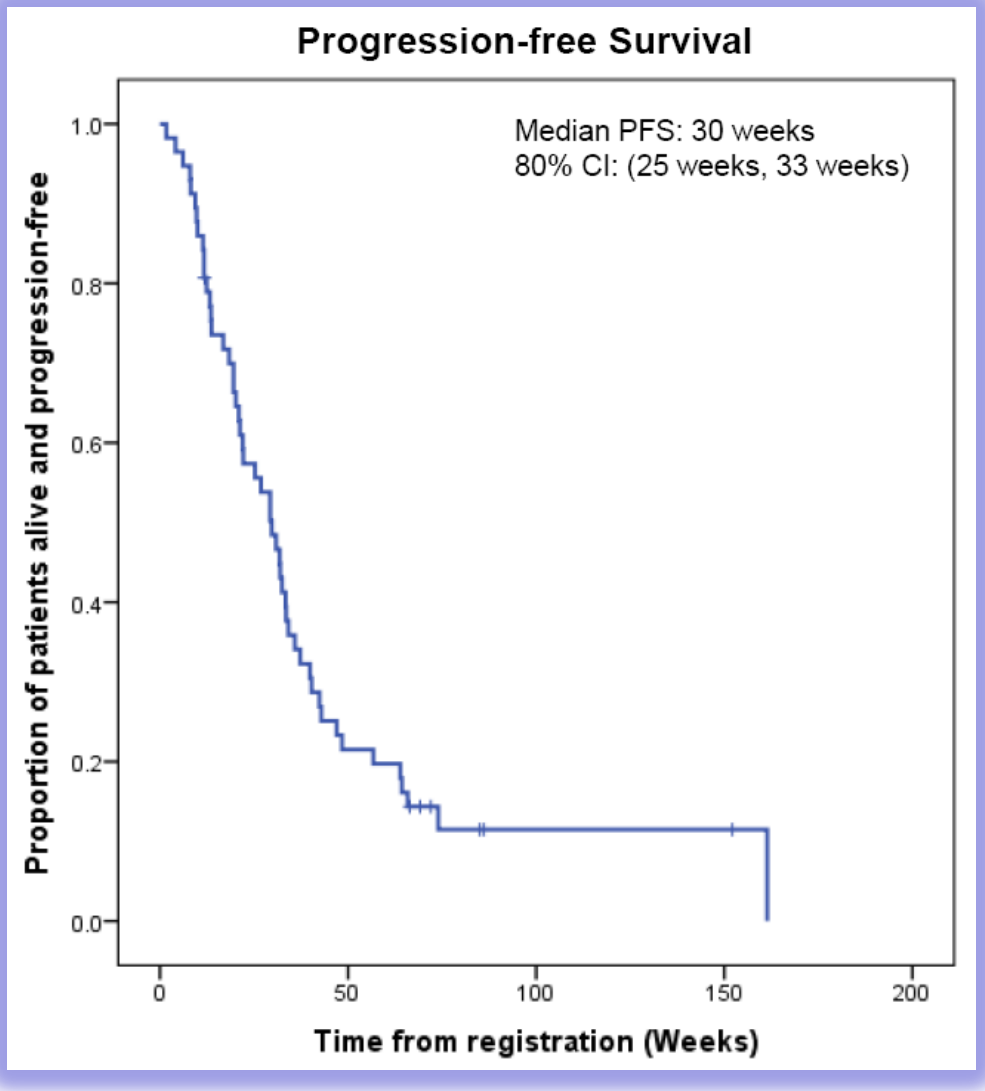
Table 1: Biopsy site using common categories (from CRF)

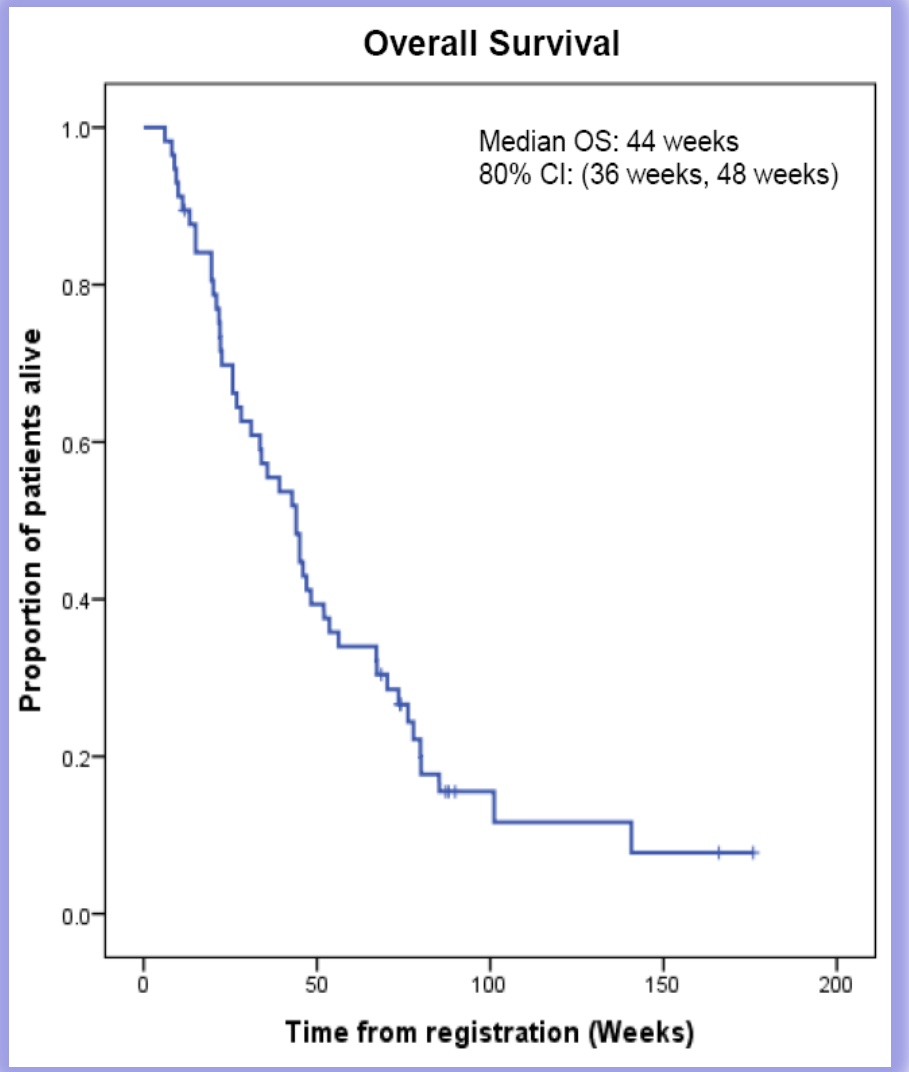
Biopsy Site	Number	% of total (205)
Other(s)	9	38%
Liver	7	29%
Bone	4	17%
Peritoneum/Omentum/Ascites	2	8%
Neck Nodes/Mass	1	4%
Abdominal Nodes	1	4%
Mediastinal Nodes	0	0%
Inguinal/Pelvic Nodes	0	0%
Pleural Effusions	0	0%
Lung	0	0%
Brain	0	0%
Total	24	100%

Table 2 Biopsy site categorised under "Other" (from CRF)

Biopsy Site	Number	% of Total
Upper gastro-intestinal tract	3	14%
Pancreatico-biliary tract	2	8%
Chest Wall or Abdomen	1	4%
Lower gastro-intestinal tract	1	4%
Axillary Nodes	1	4%
Skin	1	4%
Total	9	38%

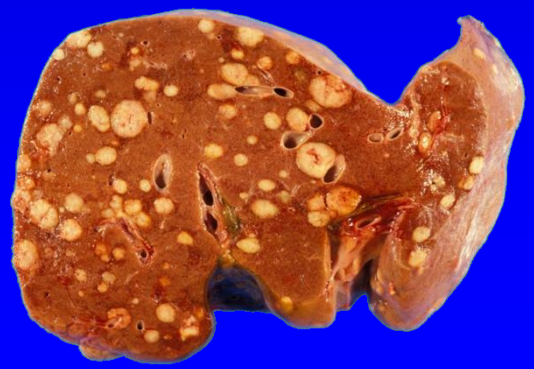
Efficacy & Response (RR 35%): CUP ONE Clinical Trial





Cancer of Unknown Primary (CUP):

UK Planned research development



Developing the UK CUP NCRN framework

Carcinoma Unknown Primary

2011	2012	2013	2014	15	…

CUP-C Platinum/5FU (F
(control a clinic

2013-14
CUP-02 – NOT approved by CRUK
CUP-T – NOT approved by CRUK
NHSE 100K - Initial Pilot planned
- on hold

n (100K-G)
irecting therapy
able

- esig constant control arm
- ble phase 1b/2/3
- central tissue collection

CUP ONE Trial evolution…..

…….. Again ??

CUP Global randomised trials
Future is international collaboration

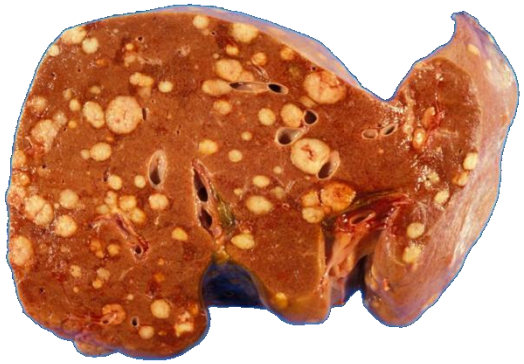
2011	2012	2013	2014	2015	…

GEFCAPI-04 site-of -origin directed Therapy rII

Pr Karim Fizazi,
Head of the Department of Cancer Medicine
Institut Gustave Roussy, University of Paris -

Original discussion in 2004 CUP-ONE !

SUPER
PeterMac / AGITG
-detailed NG Molecular analysis
leading to available targeted therapiess



CUP ONE TRIAL may define which classification(s) for treatment - predictives and prognostics - how to refine the population for a treatment hypothesis

(NGS….NHSE 100k genome project ?)

CUP: Molecular Biotype Taxonomy in 2020

- Current system organ based – assumption that cancers are more related to their organ of origin than other cancers

- **"Biotype" Classification of Cancer**

TNM will become … a personal signature

CK20+, CEA+, CK7-, TTF1-…… Site of origin

RAS13D; RAF+,MSI EGFR-amphi++ Significant Molecular aberrations

…….TxS-PLR-GemS Hierarchical Treatment

…..which also be dynamic

CUP-ONE Study Team

- **CR-UK CTU (Glasgow)**

– Chief Investigator:	Harpreet Wasan
– Translational Pathology lead	Karin Oien
– Trial Statistician:	Jim Paul
– Project Management:	Lynn McMahon;
– Pharmacovigilance:	Lindsey Connery; Katie Nocher
– Quality Assurance:	Lindsey Connery
– Trial Co-ordinators:	Pamela Fergusson; Robina Ullah; Linda Stevens; Elaine McCartney; Elizabeth Douglas; Eileen Smillie; Samantha Carmichael; Deepthi Beeravelli

- TMG Marianne Nicolson; David Bowtell; Mark Erlander; Jeff Evans; Hani Gabra, Jayson Wang

Cancer of Unknown Primary (CUP):

Thank you : Panel discussion

(+ 2 jobs for post-CST fellows in AOS/CUP research)

Dr. Harpreet S. Wasan
Department of Cancer Medicine
Hammersmith Hospital / Imperial College London
wasan@cancer.org.uk

OCT 2009